PATENT
Attorney Docket No. 09605.0016-00

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| In re Application of: | ) | |
| | ) | |
| Juan M. JIMENEZ MAYORGA et al. | ) | Group Art Unit: 1626 |
| | ) | |
| **Application No.: 10/555,286** | ) | Examiner: Loewe, Sun Jae Y. |
| | ) | |
| § 371 date: October 17, 2006 | ) | Confirmation No.: 9323 |
| | ) | |
| For: N-(2-PHENYLETHYL)SULFAMIDE DERIVATIES AS INTEGRIN α4 ANTAGONISTS | ) | ***Via EFS-WEB*** |

**Attention: Mail Stop Appeal Brief-Patents**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

## APPEAL BRIEF UNDER BOARD RULE § 41.37

In support of the Notice of Appeal filed May 15, 2009, further to Board Rule 41.37, and further to the Notice of Panel Decision from Pre-Appeal Brief Review dated September 10, 2009, Appellants present this brief and enclose herewith the fee of $540.00 required under 37 C.F.R. § 41.20(b)(2).

This Appeal Brief is being filed concurrently with a petition for an Extension of Time for five months, and the appropriate fee.

This Appeal responds to the January 16, 2009, final rejection of claims 1-10, 20, and 21, and to the Notice of Panel Decision from Pre-Appeal Brief Review dated September 10, 2009.

If any additional fees are required or if the enclosed payment is insufficient, Appellant requests that the required fees be charged to Deposit Account No. 06-0916.

## Table of Contents

## Real Party in Interest

Almirall, S.A. is the real party in interest, as evidenced by the following events and assignments: a) the inventors assigned all rights in U.S. Patent Application No. 10/555,286 to Almirall Prodesfarma, S.A. by virtue of the assignments recorded on October 5, 2006, at reel 018351, frame 0879, at reel 018352, frame 0133, and at reel 018352, frame 0160; b) Almirall Prodesfarma, S.A. changed its name to Laboratorios Almirall, S.A., which was recorded on January 22, 2007, at reel 018786, frame 0571; and c) Laboratorios Almirall S.A. changed its name to Almirall, S.A., which was recorded on March 4, 2010, at reel 024024, frame 0348.

## Related Appeals and Interferences

There are currently no other appeals or interferences, of which Appellants, Appellants' legal representative, or Assignee are aware, that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

## Status of Claims

Claims 1-15 and 20-25 are pending in this application. Claims 11-15 and 22-25 have been withdrawn by the Examiner as being directed to non-elected subject matter. The claims under examination are claims 1-10, 20, and 21. Claims 1-10, 20, and 21 have been rejected at least twice.

Appellants appeal the rejection of claims 1-10, 20, and 21.

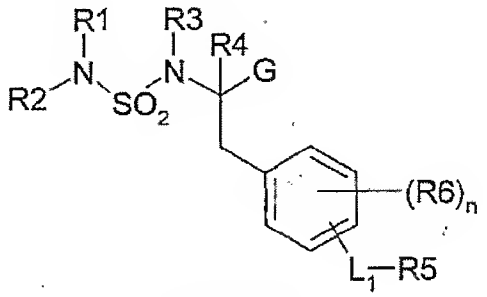
Pursuant to 37 C.F.R. § 41.37(c)(1)(viii), the attached Claim Appendix contains a clean copy of the pending claims.

## Status of Amendments

All claim amendments filed by Appellants have been entered by the Examiner. The only claim amendments by Appellants were filed in a Preliminary Amendment on November 2, 2005, and were acknowledged by the Examiner in the Office Action mailed July 22, 2008, at 2.

## Summary of Claimed Subject Matter

Claim 1 is the only independent claim in the instant application. Claim 1 is directed to a compound of formula (I):




**Formula I**

wherein:

- G is a COOH group or a tetrazolyl group;
- R1 and R2 are each independently chosen from hydrogen atoms, and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, cycloalkenyl, cycloalkenylalkyl, cycloalkenylalkenyl, cycloalkenylalkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, and heteroarylalkynyl groups;
- or R1 and R2 form, together with the nitrogen atom to which they are attached, either a 3- to 14- membered monocyclic or polycyclic heterocyclic ring system or a 5- to 14- membered heteroaryl group;

  wherein each of said 3- to 14- membered monocyclic or polycyclic heterocyclic ring system, or 5- to 14- membered heteroaryl group

comprises from 1 to 5 heteroatoms chosen from nitrogen, oxygen and sulphur;

wherein each of said alkyl, alkenyl, and alkynyl groups is independently unsubstituted or substituted with one to four substituents, wherein said one to four substituents may be the same or different and each is independently chosen from Ra;

and wherein each of said cycloalkyl, heterocyclyl, aryl and heteroaryl groups is independently unsubstituted or substituted with one to four substituents, wherein said one to four substituents may be the same or different and each is independently chosen from Rb;

- R3 and R4 are each independently chosen from hydrogen atoms and alkyl groups having from 1 to 6 carbon atoms;
- R5 is chosen from 6- to 14- membered monocyclic or polycyclic aryl groups and 5- to 14- membered monocyclic or polycyclic heteroaryl groups comprising from 1 to 5 heteroatoms chosen from nitrogen, oxygen and sulphur;

wherein each of said aryl and heteroaryl groups or moieties is independently unsubstituted or substituted with one to four substituents, wherein said one to four substituents may be the same or different and each is independently chosen from Rb;

- R6 is a group chosen from -OH, -ORc, -$NO_2$, halogen, -S(O)Rc, -$S(O)_2$Rc, -SRc, -$S(O)_2$ORc, -S(O)NRcRc -$S(O)_2$NRcRc, -NRcRc, -O(CRcRc)mNRcRc, -C(O)Rc, –$CO_2$Rc, -$CO_2$(CRcRc)mCONRcRc, -OC(O)Rc, -CN, -C(O)NRcRc, -NRcC(O)Rc, -OC(O)NRcRc, -NRcC(O)ORc, -NRcC(O)NRcRc, -CRc(N-ORc), -$CFH_2$, -$CF_2H$, -Ra, -$CF_3$, alkyl, alkenyl and alkynyl;
- n is an integer from 0 to 3
- Ra is a group chosen from alkyl, -OH, -ORc, -$NO_2$, halogen, -S(O)Rc, -$S(O)_2$Rc, -SRc, -$S(O)_2$ORc, S(O)NRcRc, -$S(O)_2$NRcRc, -NRcRc, -O(CRcRc)mNRcRc, -C(O)Rc, -$CO_2$Rc, -$CO_2$(CRcRc)mCONRcRc, -OC(O)Rc, -CN, -C(O)NRcRc, -NRcC(O)Rc, -OC(O)NRcRc, -NRcC(O)ORc, -NRcC(O)NRcRc, -CRc(N-ORc), -$CFH_2$, - $CF_2H$, -Ra, and -$CF_3$ ; wherein if two or more Rc groups are present these Rc groups may be the same or different;
- Rb is a group chosen from -OH, -ORd, -$NO_2$, halogen, -S(O)Rd, -$S(O)_2$Rd ,-SRd, -$S(O)_2$ORd,- S(O)NRdRd, -$S(O)_2$NRdRd, -NRdRd,- O(CRdRd)mNRdRd, -C(O)Rd, -$CO_2$Rd, -$CO_2$(CRdRd)mCONRdRd, -OC(O)Rd, -CN, -C(O)NRdRd, -NRdC(O)Rd, -OC(O)NRdRd, -NRdC(O)ORd, -NRdC(O)NRdRd, -CRd(N-ORd), -$CFH_2$, -$CF_2H$, -Ra, -$CF_3$, alkyl, alkenyl, $C_{2-4}$alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl; wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl groups is independently unsubstituted or substituted with one to four substituents; wherein said one to four substituents may be the same or different and each is independently chosen from Ra;

- L1 is either a direct bond or a group chosen from -N(Rc)-, -O-, -N(Rc)CO-, -CON(Rc)-, -O(CO)N(Rc)- and -N(Rc)(CO)O-;
- Rc is a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms;
- Rd is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, cycloalkenyl, cycloalkenylalkyl, cycloalkenylalkenyl, cycloalkenylalkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, or heteroarylalkynyl;

wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl and heteroaryl groups is independently unsubstituted or substituted with one to four substituents; wherein said one to four substituents may be the same or different and each is independently chosen from Re;

- Re is a group chosen from alkyl, -OH, -ORc, -$NO_2$, halogen, -S(O)Rc, -$S(O)_2$Rc, -SRc, -$S(O)_2$ORc, -S(O)NRcRc, -$S(O)_2$NRcRc, -NRcRc, -O(CRcRc)mNRcRc, -C(O)Rc, -$CO_2$Rc, -$CO_2$(CRcRc)mCONRcRc, -OC(O)Rc, -CN, -C(O)NRcRc, -NRcC(O)Rc, -OC(O)NRcRc, -NRcC(O)ORc, -NRcC(O)NRcRc, -CRc(N-ORc), -$CFH_2$, - $CF_2H$, -Ra, or -$CF_3$ ; wherein if two or more Rc groups are present these Rc groups may be the same or different;

or a pharmaceutically acceptable salt thereof;

or, when G is a carboxylic group in a compound of formula (I) or in a pharmaceutically acceptable salt of a compound of formula (I), a compound

resulting from the esterification, with an alcohol, of said carboxylic group;or a pharmaceutically acceptable salt thereof.

*See*, *e.g.*, specification at 5-7 and claim 1. The compounds of the invention "are antagonists of the α4 integrins, both the α4β1 integrin (VLA-4, "Very Late Antigen-4" or CD49d/CD29) and/or the α4β7 integrin (LPAM-1 and α4βp) , thereby blocking the binding of α4β1 to its various ligands, such as VCAM-1, osteopontin and regions of fibronectin and/or the binding of α4β7 to its various ligands, such as MadCAM-1, VCAM-1 and fibronectin." Specification at 1, ll. 4-8.

Moreover, "[t]hrough this mechanism of action .the compounds of the invention inhibit cell (e.g. leukocyte) adhesion, activation, migration, proliferation and differentiation and are useful therefore in the treatment, prevention and suppression of immune or inflammatory disorders and of other diseases mediated by α4β1 and/or α4β7 binding and/or by cell adhesion and activation, such as multiple sclerosis, asthma, allergic rhinitis, allergic conjunctivitis, inflammatory lung diseases, rheumatoid arthritis, septic arthritis, type I diabetes, rejection following organ transplantation, restenosis, rejection following autologous bone marrow transplantation, inflammatory sequelae of viral infections, atopic dermatitis, myocarditis, inflammatory bowel disease including ulcerative colitis and Crohn's disease, certain types of toxic and immune-based nephritis, contact dermal hypersensitivity, psoriasis, tumor metastasis, atherosclerosis and cerebral ischemia." *Id.* at 1, ll. 9-19.

## Grounds of Rejection

Claims 1-10, 20, and 21 stand rejected under 35 U.S.C. § 103(a) as being obvious over WO 2002/014272 in view of Patani and LaVoie, Bioisosterism: A rationale approach in drug design, *Chem. Rev.* 96:3147-3176 ("*Patani*"). Final Office Action at 2; *see also* Office Action of July 22, 2008, at 5.

## Argument

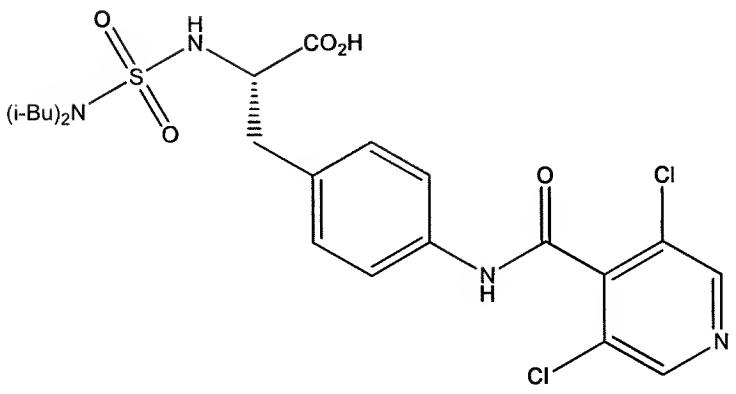
### I. The Examiner's Rejection

The Examiner rejects claims 1-10, 20, and 21 under 35 U.S.C. § 103(a) as being obvious over WO 2002/014272[1] in view of Patani and LaVoie, "Bioisosterism: A rationale approach in drug design," *Chem. Rev.* 96:3147-3176 ("*Patani*"). Final Office Action of January 16, 2009, at 2; *see also* Office Action of July 22, 2008, at 5. Appellants respectfully disagree and traverse.

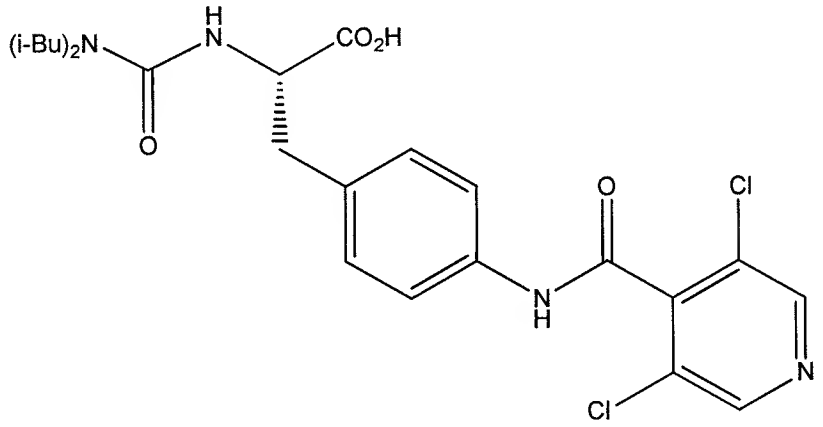
The Examiner's arguments in support of the rejection were present in the Office Action of July 22, 2008, and were not repeated or substantively modified in the Final Office Action of January 16, 2009. Therefore, Appellants will refer below mostly to the Office Action of July 22, 2008, when outlining Appellants' understanding of the instant rejection.

In response to the election requirement in the Restriction Requirement mailed May 29, 2008, Appellants' provisionally elected (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-{[(diisobutylamino)sulfonyl]amino}propionic acid, which is the product of Example 11 (structure shown below). Each of the claims under appeal (i.e., claims 1-10, 20, and 21) read on the elected species.

[1] WO 2002/014272 is a non-English language document. Appellants requested an English-language translation of this document, pursuant to M.P.E.P. § 706.02.II, in the Response filed October 22, 2008, at 4. Because the Office denied Appellants' request, Appellants submitted a certified translation of WO 2002/014272 on May 21, 2009. When so indicated in this Appeal Brief, citations to WO 2002/014272 refer to the English-language translation of WO 2002/014272 submitted by Appellants.



According to the Examiner, WO 2002/014272 teaches "compound 401470-74-4" as a VLA-4 antagonist. Office Action of July 22, 2008, at 6 and caplus abstract. The structure of compound 401470-74-4 is shown below.



The Examiner states that *Patani* teaches that sulfone (-$SO_2$-) (as in the elected species) is a bioisostere of the carbonyl group (-CO-) (as in compound 401470-74-4). Office Action of July 22, 2008, at 6. The Examiner alleges that *Patani* teaches "that sulfone moieties have been increasingly used as bioisosteres." *Id.* The Examiner further contends that "[o]ne of ordinary skill would be motivated, from the disclosure in the prior art, to make the modification required to arrive at the instant invention with reasonable expectation of success for obtaining a compound with the same activity." *Id.* at 7. In support of this rationale, the Examiner quotes the entire section from the

M.P.E.P. directed to the "obvious to try" portion of the obviousness guidelines issued after the *KSR* Supreme Court decision (M.P.E.P. § 2143.E). *Id.*

In the final Office Action mailed January 16, 2009, the Examiner alleges that "[o]ne or ordinary skill would have chosen the cited compound based on the prior art disclosure - eg. see pg. 22 [of WO 2002/014272]." Final Office Action at 3. The Examiner further asserts that "[t]he modification would have been within the level of ordinary skill (ie. see disclosure of Patani et al.)" *Id.* Finally, the Examiner states that "one of ordinary skill would have a reasonable expectation of success in obtaining an additional compound for the cited activity." *Id.* Appellants respectfully disagree and traverse.

## II. Response to Rejection

### A. The Examiner has completely ignored the relevant case law in this obviousness rejection

Appellants have presented arguments based on Federal Circuit decisions that specifically address the requirements for obviousness rejections of chemical compounds, which are particularly relevant to the instant rejection (*Eisai Co., Ltd. v. Dr. Reddy's Laboratories*, 87 U.S.P.Q.2d 1452, 533 F.3d 1353 (Fed. Cir. 2008) and *Takeda Chem. Ind., Ltd. v. Alphapharm Pty., Ltd.*, 83 U.S.P.Q.2d 1169, 492 F.3d 1350 (Fed. Cir. 2007)). To this date, however, the Examiner has not responded to these arguments, or even acknowledged Appellants' reliance on these cases. Respectfully, this type of non-engagement is not only improper under the Office's own examination guidelines (*see, e.g.*, M.P.E.P. §707.07(f)), it is also detrimental to the entire

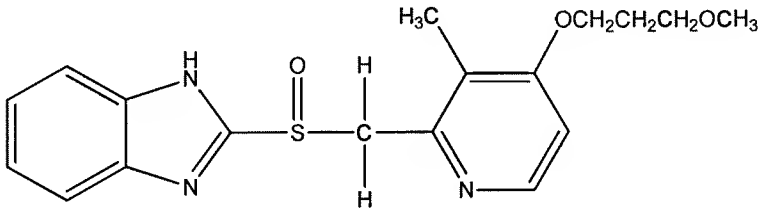
examination process and leaves applicants, in general, with few recourses when pursuing expedited prosecution[2].

i. To establish obviousness of new chemical compounds, the Examiner must (1) identify a lead compound suitable for modification, and (2) identify a reason one of ordinary skill in the art would modify that lead compound in a particular manner to arrive at the claimed compounds

a. Identification of a lead compound.

In a decision analyzing the standard for obviousness of chemical compounds, the Federal Circuit clearly indicated that the first step in this analysis is the identification of a "lead compound" that can be used as a starting point for modification to arrive to the claimed compounds. *Eisai Co., Ltd. v. Dr. Reddy's Laboratories*, 87 U.S.P.Q.2d at 1457, 533 F.3d at 1359 (underlining and italics added). This is true, even when following an "obvious to try" rationale, see section II.D below and also later in this section.

In *Eisai*, the patent at issue claimed rabeprazole (shown below) and its salts. *Eisai,* 87 U.S.P.Q.2d at 1454; 533 F.3d at 1356.

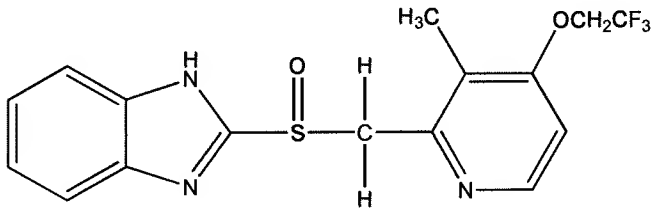



**Rabeprazole**

The compound in the prior art, "lansoprazole," shown below, had an identical formula to the patented compound, except that lansoprazole has a fluorinated group at

[2] The Examiner, exercising her discretion, also denied a request for an Examiner interview after the final Office Action because Appellants were not presenting claim amendments or data regarding unexpected results.

the 4-position of the pyridine ring whereas the substituent in the corresponding position in the patented compound is not fluorinated. *Eisai*, 87 U.S.P.Q.2d at 1455; 533 F.3d at 1357.




**Lansoprazole**

In holding the claims to the compound rabeprazole to be valid, the Federal Circuit noted that the prior art taught that the fluorinated substituent of lansoprazole provides a special path to achieving lipophilicity and that a separate reference similarly taught that fluorine-substituted groups increase lipophilicity. *Eisai*, 87 U.S.P.Q.2d at 1456; 533 F.3d at 1358. The court concluded that the record "shows no discernible reason for a skilled artisan to begin with lansoprazole only to drop the very feature, the fluorinated substituent, that gave this advantageous property." *Id.*

In addressing the standard for obviousness for chemical compounds, the Federal Circuit explicitly stated that "post-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a *lead compound*." *Id.* at 1457 (underlining and italics added). This explicit requirement followed the rationale in another post-*KSR* Federal Circuit case specifically addressing an obvious-to-try argument in the context of chemical compounds. *Takeda*, 83 U.S.P.Q.2d at 1176, 492 F.3d at 1359.

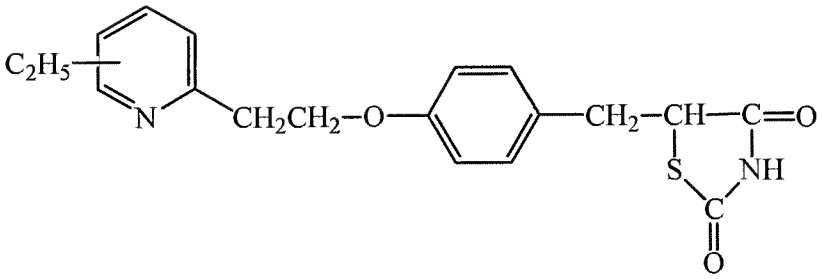
The *Takeda* court indicated that even under an obvious-to-try argument, it was still necessary to identify a lead compound. The court, citing from *KSR*, acknowledged

that "'[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.' In such circumstances, 'the fact that a combination was obvious to try might show that it was obvious under §103.'" *Id.* In analyzing arguments that the techniques to modify the known compound of the prior art to arrive at a compound within the scope of the claims "would have been 'obvious to try,'" the court stated that "[r]ather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." *Id.* With this language, the Federal Circuit is indicating that under an obvious to try approach, in order to "identify predictable solutions," it is necessary to first identify a suitable "lead compound for further investigation." The facts in *Takeda* will be discussed in more detail in the following section.

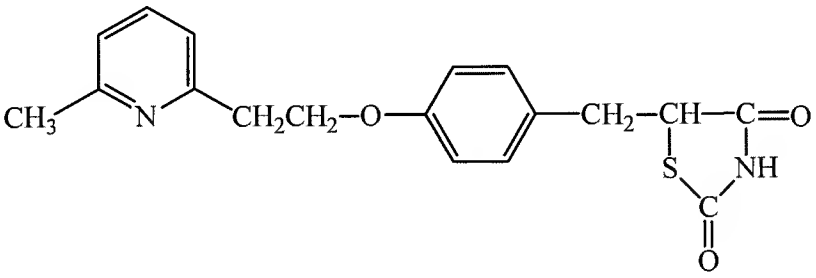
b. Specific modification of a lead compound.

Once a suitable starting point has been established, there must also be "a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention.'" *Takeda*, 83 U.S.P.Q.2d at 1174, 492 F.3d at 1356 (citations omitted). The Court explained that "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new compound." *Id.* (underlining added).

In *Takeda*, the patented compounds had the general formula (claim 1):



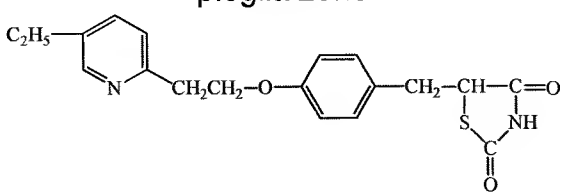
The compound in the prior art, "compound b," had an identical formula to the patented compounds, except that a methyl group, instead of an ethyl group, was attached to the pyridyl ring located on the left hand side of the molecule, as indicated in the drawing below. *Takeda*, 83 U.S.P.Q.2d at 1172, 492 F.3d at 1354.



Because the structure of the patented compounds allowed the substitution by the ethyl group on any available carbon atom in the pyridyl ring, the only difference between the prior art compound and the claimed compounds was a methylene group (–$CH_2$-) in the alkyl radical of the pyridyl ring.[3] *Id.* From a comparison of the above structures, it is evident that the degree of similarity between the prior art compound and the patented

[3] The actual commercial embodiment marketed by the patentee (pioglitazone) was also claimed in a dependent claim, and had the structure shown below. It can be seen that the only differences between pioglitazone and the prior art compound b were the replacement of the methyl group by an ethyl group and the location of the ethyl group within the pyridyl ring. *Id.* at 1772.

pioglitazone



compound is extremely high. Yet, the court in *Takeda* found the claims not obvious because there was no suggestion to prepare the claimed compounds in light of the prior art compound. *Takeda*, 83 U.S.P.Q.2d at 1176-77, 492 F.3d at 1360.

c. Overall requirements for obviousness in chemical cases

These decisions require at least that the Examiner: (1) identify a compound that would have been considered by one of ordinary skill in the art as suitable for further modification, and (2) explain the reasons why the skilled artisan would have then made the specific modifications proposed by the Examiner to arrive at the claimed invention.

In chemical cases, even an "obvious to try" rationale, as advanced by the Examiner in the instant rejection, would require the identification of a specific lead compound before one of ordinary skill in the art could even attempt to modify a compound. An "obvious to try" rationale also requires a number of other elements that the Examiner has not shown to have been met. M.P.E.P. § 2143.E.

In summary, and as will be shown below, the Examiner has not complied with any of the above requisites and Appellants will present below *three independent reasons* for withdrawal of this rejection.

**B. Independent Reason 1—The Examiner has not shown that compound 401470-74-4 would have been considered a suitable lead compound for further modification**

As discussed in *Eisai*, "a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound." *Eisai* at 1457. In chemical cases, even an "obvious to try" rationale, as advanced by the Examiner in the instant rejection, would require the identification of a specific lead compound before one of ordinary skill in the art could even attempt to modify a

compound. *Eisai*, 87 U.S.P.Q.2d at 1457, 533 F.3d at 1359 (stating that "post-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound"); *see also Takeda*, 83 U.S.P.Q.2d at 1176, 492 F.3d at 1359, and Section II.A(i)(a) above.

In the instant case, the Examiner contends that "[o]ne of ordinary skill would have chosen the cited compound based on the prior art disclosure - eg. see pg. 22." Final Office Action at 3. However, page 22 of WO 2002/014272 provides Table 1, which simply lists compound 401470-74-4 as working example no. 4, among various other compounds. No information is provided in Table 1, or anywhere else in WO 2002/014272, that would have led one of ordinary skill in the art to select compound 401470-74-4 as a suitable compound for modification from among all of the compounds disclosed in either Table 1 or WO 2002/014272. In this regard, Appellants note that Table 6 on page 30 compares $IC_{50}$ data (half maximal inhibitory concentration) obtained for various compounds, including compound 401470-74-4 (Example 4). As known in the art, a low $IC_{50}$ value is desired under the present circumstances because it indicates that a lower concentration of the test compound is needed to inhibit the relevant activity by half. Appellants note that there are eleven compounds, out of twenty-four in Table 6, with lower $IC_{50}$ values than compound 401470-74-4. That is, there are eleven compounds in Table 6 that one of ordinary skill in the art would consider *better inhibitors than compound 401470-74-4*. This fact clearly weighs against a finding that one of ordinary skill in the art would have selected compound 401470-74-4 for further modification out of all of the compounds disclosed in WO 2002/014272.

Indeed, no additional information is provided anywhere else in WO 2002/014272 to support selecting compound 401470-74-4 (the twelfth most active compound) as a lead compound.

With no evidence to support the conclusion that one of ordinary skill in the art would identify compound 401470-74-4, the Examiner has failed to meet the standards set out in *Eisai* and *Takeda* as well as the requirements for an "obvious to try" rationale. Even *Patani*, the reference cited by the Examiner, indicates *Patani's* teachings should be applied to lead compounds. Specifically, *Patani* only suggests "modification of lead compounds." *Patani* at page 3147, col. 2 (underlining added). That is, the teachings of *Patani* are applicable once one of ordinary skill in the art has identified a suitable compound as a lead compound for modification in order to obtain "safer and more clinically effective agents." *Id.* The Examiner has not explained why one of ordinary skill in the art considering the teachings in *Patani* would have considered compound 401470-74-4 a "lead compound," so that the teachings in *Patani* could be applied to its modification.

Thus, the Examiner has failed to carry her burden of proving a *prima facie* case of obviousness because she has not presented a single reason why one of ordinary skill in the art would have selected compound 401470-74-4, out of the dozens of other compounds disclosed in WO 2002/014272, as a lead compound, as clearly required by the relevant case law, and even the Examiner's own secondary reference (*Patani*).

For at least this reason, Appellants respectfully request that this rejection be reversed.

**C. Independent Reason 2—The references cited by the Examiner fail to suggest the modifications advanced by the Examiner to arrive at the claimed compounds**

As discussed in *Takeda*, "a showing that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" is also a necessary requirement in obviousness rejections of chemical compounds. *Takeda*, 83 U.S.P.Q.2d at 1174, 492 F.3d at 1356 (citations omitted). In the instant rejection, the Examiner states that *Patani* teaches that sulfone (-$SO_2$-) (present in the claimed compounds) is a bioisostere of the carbonyl group (-CO-) (present in compound 401470-74-4). Office Action of July 22, 2008, at 6. The Examiner alleges that *Patani* teaches "that sulfone moieties have been increasingly used as bioisosteres." *Id.* The Examiner asserts that "[t]he modification would have been within the level of ordinary skill (ie. see disclosure of Patani et al.)." Final Office Action at 3. Appellants understand the Examiner is arguing that, because *Patani* teaches that the sulfone moiety is a bioisostere of the carbonyl group, such knowledge would have motivated one of ordinary skill in the art to make the substitution of the carbonyl group for sulfone in compound 401470-74-4.

The Examiner's rationale ignores *Patani's* results showing that in <u>every</u> instance when the carbonyl group was substituted with sulfone, the activity of the resulting compound decreased. For example, the replacement of the carbonyl in a $LTB_4$ receptor antagonist with sulfone reduced the inhibitory activity of the compound from 85% to 79%. *Patani* at Table 39, p. 3167 (compare the activity of compound 82a, having the carbonyl group and displaying 85% inhibition, with compound 82f, having the sulfone group and showing 79% inhibition). Also, the replacement of the carbonyl group in an

euglycemic agent by a sulfone group reduced the activity of the compound from 100% to 69%. *Id.* at Table 41, p. 3168[4] (compare the activity of compound 85a, having the carbonyl group and 100% glucose normalization, with compound 85b, having the sulfone group and showing 60% glucose normalization). Appellants note that even though these arguments were presented during prosecution (response filed October 22, 2008), the Examiner has yet to respond to them, or even acknowledge them.

In any event, the teachings in *Patani*, rather than prompting one of ordinary skill in the art to substitute a carbonyl for a sulfone group as advanced by the Examiner, would discourage such substitution. Indeed, to the extent that a conclusion can be drawn from reviewing the data in *Patani* critically, one of ordinary skill in the art would surmise that other substitutions, such as C(NOH) or C(NOMe), are more promising than the substitution with a sulfone group, which is a group required in all compounds of the instant invention. *Id.* at Table 41, p. 3168 (compare the activity of compound 85a, having the carbonyl group and 100% glucose normalization, with compounds 85d and 85e, having the C(NOH) and C(NOMe) groups respectively and both showing also 100% glucose normalization, in contrast with the results with compound 85b, having the sulfone group, and showing only 60% normalization).

Regarding the standard cited above applicable in this rejection, Appellants note that *Takeda* was decided after the landmark case of *KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. 1727 (2007). Accordingly, the *Takeda* court also considered in its decision the Supreme Court's guidelines enunciated in *KSR* regarding obviousness determinations. *Takeda*, 83 USPQ2d at 1174, 482 F.3d at 1355.

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4 The results in *Patani's* Table 40 do not involve a replacement of a carbonyl group by a sulfone group and are, therefore, not relevant to the present analysis.

The Federal Circuit in *Takeda* specifically addressed the arguments on which the Examiner seems to base this rejection, namely, structural similarity (compound 401470-74-4 from WO 2002/014272 differing at least in the presence of a carbonyl instead of sulfone group from the claimed compounds) and the ability of one of ordinary skill in the art to make the modification (*Patani* allegedly teaching bioisosteres of the carbonyl group). The *Takeda* court commented that "[i]n addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure." *Takeda*, 83 USPQ2d at 1174, 482 F.3d at 1356. The Federal Circuit further explained:

> We elaborated on this requirement [to show adequate support in the prior art for the change in structure] in the case of *In re Deuel*, 51 F.3d 1552, 1558 [34 USPQ2d 1210] (Fed. Cir. 1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* . . . We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. *Id.*

*Id.* (underlining added, internal citations omitted). That is, more than the mere ability to make the modification is required to prove obviousness: the Examiner needs to show that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." Therefore, the Examiner's argument that "[t]he modification would have been within the level of ordinary skill (ie.

see disclosure of Patani et al.)" (Final Office Action at 3) is of no moment in this rejection. This is because, as shown above, the teachings in *Patani* would not have led one of ordinary skill in the art to replace a carbonyl group by a sulfone group in compound 401470-74-4.

For at least this additional reason, the Examiner has not made a *prima facie* case of obviousness and Appellants respectfully request that this rejection be reversed.

### D. Independent Reason 3—The Examiner has failed to show the required elements of an "obvious to try" rationale

a. Even an "obvious to try" rejection of chemical compounds requires identification of a lead compound

In chemical cases, even an "obvious to try" rationale, as advanced by the Examiner in the instant rejection, would require the identification of a specific lead compound before one can attempt to perform the modifications necessary to arrive at the claimed compounds. *See Eisai*, 87 U.S.P.Q.2d at 1457, 533 F.3d at 1359 (stating that "post-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound"); *see also Takeda*, 83 U.S.P.Q.2d at 1176, 492 F.3d at 1359.

As mentioned above, the Examiner has provided no evidence that one of ordinary skill in the art would have chosen to modify compound 401470-74-4, from among all compounds disclosed in WO 2002/014272.

b. The Examiner has not provided additional required elements of an "obvious to try" rejection

To reject a claim based on an "obvious to try" rationale, the Examiner must articulate, among other things, (1) a finding that at the time of the invention, there had

been a recognized problem or need in the art, and (2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem. *See, e.g.*, M.P.E.P. § 2143.E.

In the present case, the Examiner has failed at least to provide "a finding that at the time of the invention, there had been a recognized problem or need in the art." That is, the Examiner has pointed to no evidence indicating that the art considered the compounds of WO 2002/014272 unsatisfactory for their intended purpose and that new, different compounds were needed.

Additionally, the Examiner has failed to provide the identity of the set of "finite number of identified, predictable potential solutions to a recognized need or problem." The record is entirely silent with respect to this issue.

For at least these reasons, the Examiner has not made a *prima facie* case of obviousness and Appellants respectfully request that this rejection be reversed.

## III. Conclusion

For the reasons given above, pending claims 1-10, 20, and 21 are allowable and reversal of the Examiner's rejection is respectfully requested.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: March 9, 2010

By: _____

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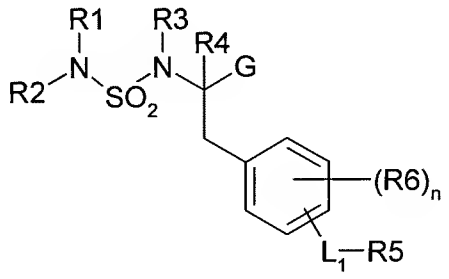
## Claims Appendix to Appeal Brief Under Rule 41.37(c)(1)(viii)

1. (Previously Presented) A compound of formula (I):




(I)

wherein:

- G is a COOH group or a tetrazolyl group;
- R1 and R2 are each independently chosen from hydrogen atoms, and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, cycloalkenyl, cycloalkenylalkyl, cycloalkenylalkenyl, cycloalkenylalkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, and heteroarylalkynyl groups;

- or R1 and R2 form, together with the nitrogen atom to which they are attached, either a 3- to 14- membered monocyclic or polycyclic heterocyclic ring system or a 5- to 14- membered heteroaryl group;

wherein each of said 3- to 14- membered monocyclic or polycyclic heterocyclic ring system, or 5- to 14- membered heteroaryl group comprises from 1 to 5 heteroatoms chosen from nitrogen, oxygen and sulphur;

wherein each of said alkyl, alkenyl, and alkynyl groups is independently unsubstituted or substituted with one to four substituents, wherein said one to four substituents may be the same or different and each is independently chosen from Ra;

and wherein each of said cycloalkyl, heterocyclyl, aryl and heteroaryl groups is independently unsubstituted or substituted with one to four substituents, wherein said one to four substituents may be the same or different and each is independently chosen from Rb;

- R3 and R4 are each independently chosen from hydrogen atoms and alkyl groups having from 1 to 6 carbon atoms;
- R5 is chosen from 6- to 14- membered monocyclic or polycyclic aryl groups and 5- to 14- membered monocyclic or polycyclic heteroaryl groups comprising from 1 to 5 heteroatoms chosen from nitrogen, oxygen and sulphur;

wherein each of said aryl and heteroaryl groups or moieties is independently unsubstituted or substituted with one to four substituents, wherein said one to four substituents may be the same or different and each is independently chosen from Rb;

- R6 is a group chosen from -OH, -ORc, -$NO_2$, halogen, -S(O)Rc, -$S(O)_2$Rc, -SRc, -$S(O)_2$ORc, -S(O)NRcRc -$S(O)_2$NRcRc, -NRcRc, -O(CRcRc)mNRcRc, -C(O)Rc, –$CO_2$Rc, -$CO_2$(CRcRc)mCONRcRc, -OC(O)Rc, -CN, -C(O)NRcRc, -NRcC(O)Rc, -OC(O)NRcRc, -NRcC(O)ORc, -NRcC(O)NRcRc, -CRc(N-ORc), -$CFH_2$, -$CF_2H$, -Ra, -$CF_3$, alkyl, alkenyl and alkynyl;
- n is an integer from 0 to 3
- Ra is a group chosen from alkyl, -OH, -ORc, -$NO_2$, halogen, -S(O)Rc, -$S(O)_2$Rc, -SRc, -$S(O)_2$ORc, S(O)NRcRc, -$S(O)_2$NRcRc, -NRcRc, -O(CRcRc)mNRcRc, -C(O)Rc, -$CO_2$Rc, -$CO_2$(CRcRc)mCONRcRc, -OC(O)Rc, -CN, -C(O)NRcRc, -NRcC(O)Rc, -OC(O)NRcRc, -NRcC(O)ORc, -NRcC(O)NRcRc, -CRc(N-ORc), -$CFH_2$, - $CF_2H$, -Ra, and -$CF_3$ ; wherein if two or more Rc groups are present these Rc groups may be the same or different;
- Rb is a group chosen from -OH, -ORd, -$NO_2$, halogen, -S(O)Rd, -$S(O)_2$Rd ,-SRd, -$S(O)_2$ORd,- S(O)NRdRd, -$S(O)_2$NRdRd, -NRdRd,- O(CRdRd)mNRdRd, -C(O)Rd, -$CO_2$Rd, -$CO_2$(CRdRd)mCONRdRd, -OC(O)Rd, -CN, -C(O)NRdRd, -NRdC(O)Rd, -OC(O)NRdRd, -NRdC(O)ORd, -NRdC(O)NRdRd, -CRd(N-ORd), -$CFH_2$, -$CF_2H$, -Ra, -$CF_3$, alkyl, alkenyl, $C_{2-4}$alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl; wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl groups is independently unsubstituted or substituted with one to four substituents; wherein said one to four substituents may be the same or different and each is independently chosen from Ra;

- L1 is either a direct bond or a group chosen from -N(Rc)-, -O-, -N(Rc)CO-, -CON(Rc)-, -O(CO)N(Rc)- and -N(Rc)(CO)O-;
- Rc is a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms;
- Rd is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, cycloalkenyl, cycloalkenylalkyl, cycloalkenylalkenyl, cycloalkenylalkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, or heteroarylalkynyl;

wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl and heteroaryl groups is independently unsubstituted or substituted with one to four substituents; wherein said one to four substituents may be the same or different and each is independently chosen from Re;

- Re is a group chosen from alkyl, -OH, -ORc, -$NO_2$, halogen, -S(O)Rc, -$S(O)_2$Rc, -SRc, -$S(O)_2$ORc, -S(O)NRcRc, -$S(O)_2$NRcRc, -NRcRc, -O(CRcRc)mNRcRc, -C(O)Rc, -$CO_2$Rc, -$CO_2$(CRcRc)mCONRcRc, -OC(O)Rc, -CN, -C(O)NRcRc, -NRcC(O)Rc, -OC(O)NRcRc, -NRcC(O)ORc, -NRcC(O)NRcRc, -CRc(N-ORc), -$CFH_2$, - $CF_2H$, -Ra, or -$CF_3$ ; wherein if two or more Rc groups are present these Rc groups may be the same or different;

or a pharmaceutically acceptable salt thereof;

or, when G is a carboxylic group in a compound of formula (I) or in a pharmaceutically acceptable salt of a compound of formula (I), a compound

resulting from the esterification, with an alcohol, of said carboxylic group;or a pharmaceutically acceptable salt thereof.

2. (Previously Presented) A compound according to claim 1, wherein G is a COOH group or a compound resulting from the esterification, with an alcohol, of the COOH group.

3. (Previously Presented) A compound according to claim 1, wherein R3 and R4 are hydrogen atoms.

4. (Previously Presented) A compound according to claim 1, wherein R1 and R2 are each independently chosen from hydrogen atoms, alkyl, cycloalkyl, heterocyclylalkyl, aryl, arylalkyl, and heteroarylalkyl groups, wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl groups is independently unsubstituted or substituted;

or R1 and R2 form, together with the nitrogen atom to which they are attached, a 5- to 8- membered monocyclic heterocyclic ring system wherein said ring system comprises from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulphur; and wherein said ring system is unsubstituted or substituted.

5. (Previously Presented) A compound according to claim 1, wherein R5 is chosen from a 6- to 14- membered monocyclic or polycyclic aryl and a 5- to 14- membered monocyclic or polycyclic heteroaryl group comprising from 1 to 5 heteroatoms chosen from nitrogen, oxygen and sulphur; wherein each of said aryl and heteroaryl groups is independently unsubstituted or substituted.

6. (Previously Presented) A compound according to claim 5, wherein each of said aryl and heteroaryl groups is independently unsubstituted or substituted by one or more halogen atoms.

7. (Previously Presented) A compound according to claim 1, wherein L1 is a group chosen from -NH-, -O- and -NHCO-.

8. (Previously Presented) A compound according to claim 1, wherein R5–L1- is chosen from benzamide, isonicotinamide, 2,6-naphthyridin-1-ylamino, 2,7-naphthyridin-1-ylamino; 2,6-naphthyridin-1-yloxy and 2,7-naphthyridin-1-yloxy wherein said groups are unsubstituted or substituted.

9. (Previously Presented) A compound according to claim 1, wherein n is zero.

10. (Previously Presented) A compound according to claim 1 chosen from:

- (2*S*)-2-{[(tert-butylamino)sulfonyl]amino}-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propionic acid
- Methyl (2*S*)-2-(*N*-benzylaminosulfonilamino)-3-[4-(2,6-dichlorobenzoylamino)phenyl]propionate
- (2*S*)-2-(*N*-benzylaminosulfonilamino)-3-[4-(2,6-dichlorobenzoylamino)phenyl]propionic acid
- Methyl (2*S*)-3-{4-[(2,6-dichlorobenzoyl)amino]phenyl}-2-{[(dimethylamino)sulfonyl]amino} propionate
- (2*S*)-3-{4-[(2,6-dichlorobenzoyl)amino]phenyl}-2-{[(dimethylamino)sulfonyl]amino} propionic acid

- Methyl (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-{[(dimethylamino)sulfonyl]amino}propionate
- (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-{[(dimethylamino)sulfonyl]amino}propionic acid
- Methyl (2*S*)-3-(4-{[1-(2,6-dichlorophenyl)methanoyl]amino}phenyl)-2-(piperidine-1-sulfonylamino)propionate
- (2*S*)-3-(4-{[1-(2,6-dichlorophenyl)methanoyl]amino}phenyl)-2-(piperidine-1-sulfonylamino)propionic acid
- Methyl (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-{[(diisobutylamino)sulfonyl]amino}propionate
- (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-{[(diisobutylamino)sulfonyl]amino}propionic acid
- Methyl (2*S*)-2-({[benzyl(ethyl)amino]sulfonyl}amino)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propionate
- (2*S*)-2-{[(benzylethylamino)sulfonyl]amino}-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propionic acid
- Methyl (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-{[(dibutylamino)sulfonyl]amino}propionate
- (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-{[(dibutylamino)sulfonyl]amino}propionic acid
- Methyl (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-({[[2-(3,4-dimethoxyphenyl)ethyl]isobutylamino]sulfonyl}amino)propionate

- (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-({[[2-(3,4-dimethoxyphenyl)ethyl]isobutylamino]sulfonyl}amino)propionic acid
- Methyl (2*S*)-2-({[bis(thien-2-ylmethyl)amino]sulfonyl}amino)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propionate
- (2*S*)-2-({[bis(thien-2-ylmethyl)amino]sulfonyl}amino)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propionic acid
- Methyl (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-({[methyl(2-pyridin-2-ylethyl)amino]sulfonyl}amino)propionate
- (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-({[methyl(2-pyridin-2-ylethyl)amino]sulfonyl}amino)propionic acid
- Methyl (2*S*)-2-{[(cyclohexylmethylamino)sulfonyl]amino}-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propionate
- (2*S*)-2-{[(cyclohexylmethylamino)sulfonyl]amino}-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propionic acid
- Methyl (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-({[(3-methylbutyl)(thien-2-ylmethyl)amino]sulfonyl}amino)propionate
- (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-({[(3-methylbutyl)(thien-2-ylmethyl)amino]sulfonyl}amino)propionic acid
- Methyl (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-[(piperidin-1-ylsulfonyl)amino]propionate
- (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-[(piperidin-1-ylsulfonyl)amino]propionic acid

- Methyl (2*S*)-2-[(azepan-1-ylsulfonyl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propionate
- (2*S*)-2-[(azepan-1-ylsulfonyl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propionic acid
- Methyl (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-[(morpholin-4-ylsulfonyl)amino]propionate
- (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-[(morpholin-4-ylsulfonyl)amino]propionic acid
- Methyl (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-[(thiomorpholin-4-ylsulfonyl)amino]propionate
- (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-[(thiomorpholin-4-ylsulfonyl)amino]propionic acid
- Methyl (2*S*)-2-{[(dimethylamino)sulfonyl]amino}-3-[4-(2,6-naphthyridin-1-yloxy)phenyl]propionate
- (2*S*)-2-{[(dimethylamino)sulfonyl]amino}-3-[4-(2,6-naphthyridin-1-yloxy)phenyl]propionic acid
- Methyl (2*S*)-2-{[(diisobutylamino)sulfonyl]amino}-3-[4-(2,6-naphthyridin-1-yloxy)phenyl]propionate
- (2*S*)-2-{[(diisobutylamino)sulfonyl]amino}-3-[4-(2,6-naphthyridin-1-yloxy)phenyl]propionic acid
- Methyl (2*S*)-2-{[(diisobutylamino)sulfonyl]amino}-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]propionate

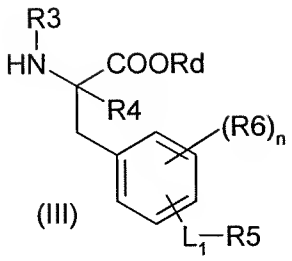
- (2*S*)-2-{[(diisobutylamino)sulfonyl]amino}-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]propionic acid
- Methyl (2*S*)-3-{4-[(2,6-dichlorobenzoyl)amino]phenyl}-2-{[(2,6-dimethylpiperidin-1-yl)sulfonyl]amino}propionate
- (2*S*)-3-{4-[(2,6-dichlorobenzoyl)amino]phenyl}-2-{[(2,6-dimethylpiperidin-1-yl)sulfonyl]amino}propionic acid
- Methyl (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-{[(diisopropylamino)sulfonyl]amino}propionate
- (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-{[(diisopropylamino)sulfonyl]amino}propionic acid
- Methyl (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-{[(2,6-dimethylpiperidin-1-yl)sulfonyl]amino}propionate
- (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-{[(2,6-dimethylpiperidin-1-yl)sulfonyl]amino}propionic acid
- Methyl (2*S*)-2-{[(dimethylamino)sulfonyl]amino}-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]propionate
- (2*S*)-2-{[(dimethylamino)sulfonyl]amino}-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]propionic acid
- Methyl (2*S*)-2-{[(diisopropylamino)sulfonyl]amino}-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]propionate
- (2*S*)-2-{[(diisopropylamino)sulfonyl]amino}-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]propionic acid

- Methyl (2*S*)-2-({[cyclohexyl(isopropyl)amino]sulfonyl}amino)-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]propionate
- (2*S*)-2-({[cyclohexyl(isopropyl)amino]sulfonyl}amino)-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]propionic acid
- Methyl (2S)-2-{[(diisopropylamino)sulfonyl]amino}-3-[4-(2,6-naphthyridin-1-yloxy)phenyl]propionate
- (2S)-2-{[(diisopropylamino)sulfonyl]amino}-3-[4-(2,6-naphthyridin-1-yloxy)phenyl]propionic acid
- Methyl (2S)-2-{[(diisopropylamino)sulfonyl]amino}-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]propionate
- (2S)-2-{[(diisopropylamino)sulfonyl]amino}-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]propionic acid
- Methyl (2*S*)-2-{[(2,6-dimethylpiperidin-1-yl)sulfonyl]amino}-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]propionate
- (2*S*)-2-{[(2,6-dimethylpiperidin-1-yl)sulfonyl]amino}-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]propionic acid
- Methyl (2*S*)-2-{[(2,6-dimethylpiperidin-1-yl)sulfonyl]amino}-3-[4-(2,6-naphthyridin-1-yloxy)phenyl]propionate
- (2*S*)-2-{[(2,6-dimethylpiperidin-1-yl)sulfonyl]amino}-3-[4-(2,6-naphthyridin-1-yloxy)phenyl]propionic acid
- Methyl (2*S*)-2-({[benzyl(isopropyl)amino]sulfonyl}amino)-3-{4-[(2,6-dichlorobenzoyl)amino]phenyl}propionate

- (2*S*)-2-({[benzyl(isopropyl)amino]sulfonyl}amino)-3-{4-[(2,6-dichlorobenzoyl)amino]phenyl}propionic acid
- Methyl (2*S*)-2-({[benzyl(isopropyl)amino]sulfonyl}amino)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propionate
- (2S)-2-({[benzyl(isopropyl)amino]sulfonyl}amino)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propionic acid
- Methyl (2*S*)-2-({[isopropyl(thien-2-ylmethyl)amino]sulfonyl}amino)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propionate
- (2*S*)-2-({[isopropyl(thien-2-ylmethyl)amino]sulfonyl}amino)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propionic acid
- Methyl (2*S*)-2-({[isopropyl(thien-2-ylmethyl)amino]sulfonyl}amino)-3-{4-[(3,5-dichlorobenzoyl)amino]phenyl}propionate
- (2*S*)-2-({[isopropyl(thien-2-ylmethyl)amino]sulfonyl}amino)-3-{4-[(3,5-dichlorobenzoyl)amino]phenyl}propionic acid
- Methyl (2*S*)-3-{4-[(2,6-dichloroisonicotinoyl)amino]phenyl}-2-[({isobutyl[(1*S*)-1-phenylethyl]amino}sulfonyl)amino]propionate
- (2*S*)-3-{4-[(2,6-dichloroisonicotinoyl)amino]phenyl}-2-[({isobutyl[(1*S*)-1-phenylethyl]amino}sulfonyl)amino]propionic acid
- Methyl (2*S*)-2-({[cyclopentyl(isopropyl)amino]sulfonyl}amino)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propionate
- (2*S*)-2-({[cyclopentyl(isopropyl)amino]sulfonyl}amino)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propionic acid

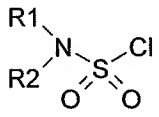
- Methyl (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-({[isobutyl(isopropyl)amino]sulfonyl}amino)propionate
- (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-({[isobutyl(isopropyl)amino]sulfonyl}amino)propionic acid
- Methyl (2*S*)-2-({[cyclohexyl(isopropyl)amino]sulfonyl}amino)-3-[4-(2,6-naphthyridin-1-yloxy)phenyl]propionate
- (2*S*)-2-({[cyclohexyl(isopropyl)amino]sulfonyl}amino)-3-[4-(2,6-naphthyridin-1-yloxy)phenyl]propionic acid
- Methyl (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-[({isobutyl[(1R)-1-phenylethyl]amino}sulfonyl)amino]propionate
- (2*S*)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}-2-[({isobutyl[(1R)-1-phenylethyl]amino}sulfonyl)amino]propionic acid
- Methyl (2*S*)-2-({[methyl(phenyl)amino]sulfonyl}amino)-3-{4-[(2,6-dichlorobenzoyl)amino]phenyl}propionate
- (2*S*)-2-({[methyl(phenyl)amino]sulfonyl}amino)-3-{4-[(2,6-dichlorobenzoyl)amino]phenyl}propionic acid
- Methyl (2S)-({[2-(phenylsulfonyl)phenyl]amino}sulfonyl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propionate; and
- (2S)-({[2-(phenylsulfonyl)phenyl]amino}sulfonyl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propionic acid;
- or a pharmaceutically acceptable salt thereof.

11. (Withdrawn) A process for producing a compound of claim 1, comprising reacting an amine of formula (III):




(III)

with a corresponding sulfamoyl chloride of formula (IV):

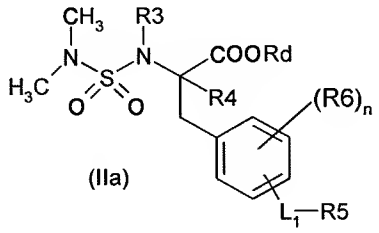



(IV)

to produce a compound of formula (I); and

optionally producing a pharmaceutically acceptable salt of a compound of formula (I).

12. (Withdrawn) A process for producing a compound of claim 1, comprising reacting an amine of formula (IIa):




(IIa)

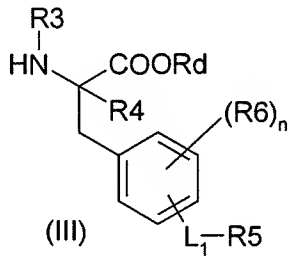
with an amine of formula (V)

(V)

to produce a compound of formula (I); and

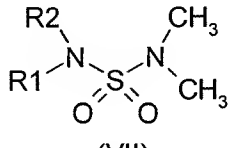
optionally producing a pharmaceutically acceptable salt of a compound of formula (I).

13. (Withdrawn) A process for producing a compound of claim 1, comprising reacting an amine of formula (III):



(III)

with a sulfamide of formula (VII):



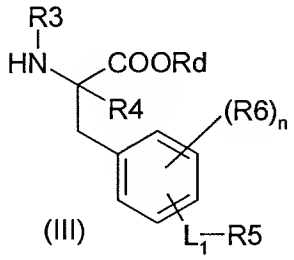
(VII)

to produce a compound of formula (I); and

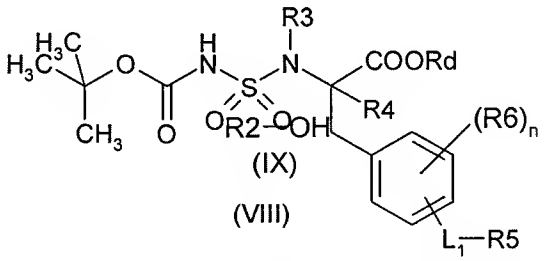
optionally producing a pharmaceutically acceptable salt of a compound of formula (I).

14. (Withdrawn) A process for producing a compound of claim 1, comprising:

reacting an amine of formula (III):




with tert-butanol and chlorosulfonyl isocyanate to yield the sulfamide of formula (VIII);



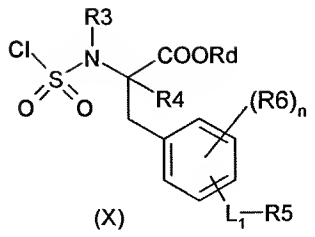

reacting the sulfamide of formula (VIII) with an alcohol of formula (IX)

to produce a compound of formula (I); and

optionally producing a pharmaceutically acceptable salt of a compound of formula (I).

15. (Withdrawn) A process for producing a compound of claim 1, comprising

reacting an amine of formula (X):




(X)

with an amine of formula (V)


(V)

to produce a compound of formula (I); and

optionally producing a pharmaceutically acceptable salt of a compound of formula (I).

16. (Cancelled)

17. (Cancelled)

18. (Cancelled)

19. (Cancelled)

20. (Previously Presented) A pharmaceutical composition comprising an effective amount of a compound as defined in claim 1, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

21. (Previously Presented) A compound or a pharmaceutically acceptable salt thereof as defined in claim 1, for use in a method of treatment of a subject afflicted with a pathological condition susceptible to amelioration by antagonism of $\alpha 4\beta 1$ and/or $\alpha 4\beta 7$ integrins.

22. (Withdrawn) A method for treating a subject afflicted with a pathological condition susceptible to amelioration by antagonism of $\alpha 4\beta 1$ and/or $\alpha 4\beta 7$ integrins, comprising administering to said subject an effective amount of a compound as defined in claim 1.

23. (Withdrawn) A method according to claim 22, wherein the pathological condition is susceptible to amelioration by the inhibition or prevention of cell adhesion processes mediated by $\alpha 4\beta 1$ and/or $\alpha 4\beta 7$ integrins.

24. (Withdrawn) A method according to claim 22, wherein the pathological condition is an immune or inflammatory disease or disorder susceptible to amelioration by antagonism of $\alpha 4\beta 1$ and/or $\alpha 4\beta 7$ integrins.

25. (Withdrawn) A method according to claim 22, wherein the pathological condition or disease is chosen from multiple sclerosis, asthma, allergic rhinitis, allergic conjunctivitis, an inflammatory lung disease, rheumatoid arthritis, polydermatomyositis, septic arthritis, type I diabetes, rejection following organ transplantation, restenosis, rejection following autologous bone marrow transplantation, inflammatory sequelae of viral infections, atopic dermatitis, myocarditis, inflammatory bowel disease including ulcerative colitis and Chron's

disease, certain types of toxic and immune-based nephritis, contact dermal hypersensitivity, psoriasis, tumor metastasis, atherosclerosis and cerebral ischemia.

**Evidence Appendix to Appeal Brief Under Rule 41.37(c)(1)(ix)**

The rejection on appeal is based in part on WO 2002/014272, which is a Japanese language document. While the Examiner states that "the record is clear as to the precise facts relied upon in support of the rejection" and considered that an English-language translation was not necessary (Final Office Action of January 16, 2009, at pages 2-3), Appellants nonetheless submitted to the Office a certified English-language translation of WO 2002/014272 on May 21, 2009. A copy of this translation is attached to this Appeal Brief.

**Related Proceedings Appendix to Appeal Brief Under Rule 41.37(c)(1)(x)**

None.